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Nasal congestion model in Brown Norway rats and the effects of some H_1-antagonists

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Abstract

The aim of this study was to develop and characterize a new model for evaluating nasal congestion in rats by using whole body plethysmography (WBP)-free moving application. Brown Norway rats were sensitized with 10% toluene-2, 4-diisocyanate (TDI) solution, and nasal congestion was provoked with 5% TDI. An increase in the enhanced pause (Penh) was recognized after being challenged with TDI. In addition, a significant increase in the Penh was observed following the intranasal application of histamine in TDI sensitized rats. Histamine H_1 antagonists, such as chlorpheniramine and ketotifen suppressed the increase of Penh during the early-phase response. On the other hand, epinastine suppressed the increase of Penh in both the early and late phase responses. In conclusion, we developed an allergic rhinitis model that includes nasal congestion symptoms in Brown Norway rats, and this model may be useful for evaluating the effects of drugs on nasal congestion.

Keywords: Nasal congestion; TDI; Penh; Histamine; Chlorpheniramine; Ketotifen; Epinastine; Brown Norway rats

1. Introduction

Allergic rhinitis is an inflammatory disease of the upper airways, affecting approximately 20% of the world population [1]. The main symptoms of allergic rhinitis are observed in the early-phase and the late-phase of the disease, the early-phase response occurs within a few minutes of antigen exposure and subsides after 30–90 min. In contrast, the late-phase reaction begins around 4–8 h after the early-phase response [2]. One of the typical symptoms in allergic rhinitis is nasal congestion. Nasal congestion associated with allergic rhinitis may be due to the increased nasal blood flow causing increased filling and distention of the venous erectile tissue, which develops an edematous swelling of the nasal mucosal membrane [3]. Since nasal congestion in human beings is a subjective symptom, it is therefore difficult to evaluate in animals. A nasal congestion model has been reported using acoustic rhinometry in guinea pigs, cats and dogs, which was evaluated by observing the decrease in the size of the nasal cavity [4–6]. In addition, there was a report regarding a model using the double-flow plethysmograph system in guinea pigs, which measured the specific airway resistance and the respiratory rate [7]. In these models, however, anesthetics must be given to the animals and the fixation of them is required. In these procedures, stress may also influence the data.

Toluene-2, 4-diisocyanate (TDI) is used in the plastics industry (National Toxicology Program, 2002), and

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this compound is considered to be a causative agent for allergic respiratory diseases, including not only pulmonary diseases such as asthma and hypersensitive pneumonitis, but also rhinitis. In the guinea pig-TDI sensitized model, both rhinorrhea and sneezing were observed. In addition, large numbers of eosinophiles were often observed in rhinorrhea from TDI sensitized guinea pigs and rats [8,9].

The purpose of this study was to develop a new nasal congestion model using TDI by measuring whole body plethysmography (WBP)-free moving application, which can estimate under the waking and unrestrained conditions in animals. In addition, it was also examined whether or not the increase in enhanced pause (Penh) caused by TDI challenge is inhibited by pretreating with some histamine H_1-antagonists.

2. Materials and methods

2.1. Animals

Six-week-old male Brown Norway (BN) rats were obtained from Seac Yoshitomi Ltd, Japan. The animals were housed in an air-conditioned room, maintained at 24 ± 2 °C, with a humidity of $55 \pm 15\%$. The rats were given a standard laboratory rodent food (Oriental Yeast, Tokyo, Japan) and water ad libitum. Rats were 6 weeks old at the start of the experiments.

2.2. Reagents and drugs

The following reagents were obtained from the sources shown in parentheses: histamine dihydrochloride (Sigma, St. Louis, MO, USA), TDI (Wako, Tokyo, Japan) and ethyl acetate (Wako). TDI was dissolved in ethyl acetate to a concentration of 10% for sensitization and to a concentration of 5% for challenge. Chlorpheniramine maleate (Sigma), ketotifen fumarate (Novartis, Basel, Switzerland), and epinastine hydrochloride (Böheringer Ingelheim, Ingelheim, Germany), were suspended in 5% gum arabic and were administered orally.

2.3. Sensitization

Sensitization to TDI was performed according to the method described by Tanaka et al. [8] with a slight modification. Rats were sensitized by the intranasal application of 10% TDI solution in ethyl acetate once a day for 5 consecutive days. Two days later, the rats were sensitized with TDI again for 5 days (Fig. 1).

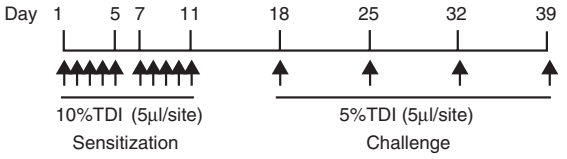

Fig. 1. Protocol for TDI sensitization and challenge. The animals were sensitized with 10% TDI for 5 consecutive days and two days later, the rats were sensitized again for 5 days. On days 18 to 39, the rats were challenged with 5% TDI once a week.

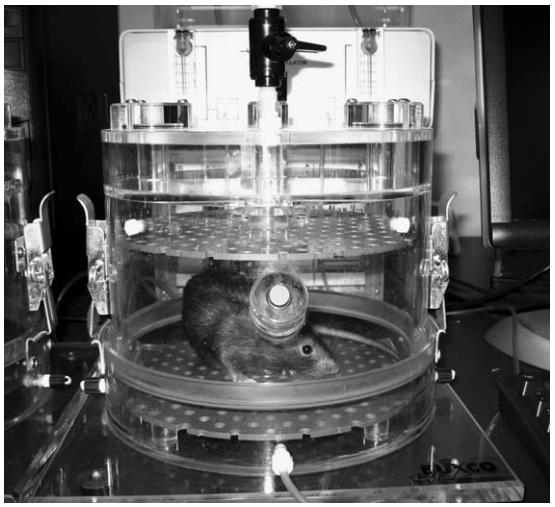

Fig. 2. A photo of the animals in whole body plethysmography-free moving application.

2.4. The measurement method for Penh in unrestrained WBP-free moving application

The animal is entirely enclosed in the animal chamber, and free to move around within an enclosed space (Fig. 2). When the animal inspires, air is removed from the chamber, and enters the lungs, driving the chamber pressure down. At the same time, however, the lungs expanded, increasing the chamber pressure. The difference between these two processes creates the respiratory signal that is measured in WBP. This respiratory signal is caused by pressure changes in the animal chamber during the respiratory cycle of the animal. Respiratory signals were analysed to obtain values for frequency of breathing (f), inspiratory time (Ti), expiratory time (T_e),

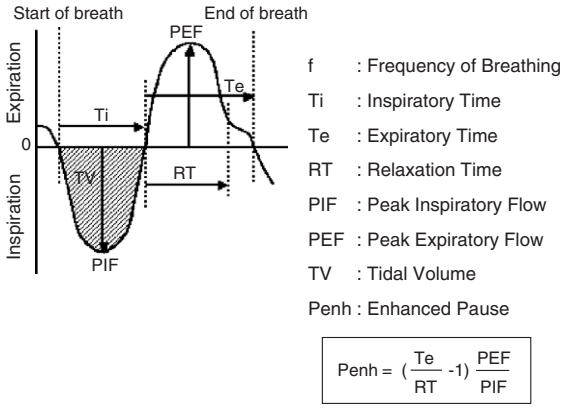

Fig. 3. Computation of the parameters measured using whole body plethysmography.